Shiraz E-Med J. 2020 August; 21(8):e96612. doi: 10.5812/semj.96612.

Published online 2020 April 6. **Research Article**

Assessment of the Relationship Between Iron Overload Based on Cardiac T2* MRI and Fragmented QRS in Beta-Thalassemia Major Patients

Yazdan Ghandi [1,*], Danial Habibi [2] and Aziz Eghbali [3]

[1] Pediatric Cardiologist, Amir Kabir Hospital, Arak University of Medical Sciences, Arak, Iran
[2] Department of Biostatistics and Epidemiology, Faculty of Health, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Pediatric Oncology, Ali Asghar Hospital, Tehran University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Associate Professor, Pediatric Cardiologist, Amir Kabir Hospital, Arak University of Medical Sciences, Arak, Iran. Email: drghandi1351@gmail.com

Received 2019 July 24; **Revised** 2019 October 12; **Accepted** 2019 October 19.

Abstract

Background: Cardiac involvement in beta-thalassemia major patients is an important cause of mortality. Therefore, in these patients, timely diagnosis of cardiac disorder is essential.
Objectives: The present study aimed at determining the association between cardiac iron overload and fragmented QRS (fQRS).
Methods: This cross-sectional study was conducted on 40 β-TM patients, aged 5 - 40 years. The presence of fQRS was evaluated in 12-lead surface electrocardiograms. Cardiac T2* MRI was performed to determine the iron overload. The patients were divided into four groups of chelation therapy.
Results: The mean age of patients was reported to be 22.50 $\pm$ 6.75 years. The groups showed no significant difference regarding gender, age, or left ventricular ejection fraction. The presence of fQRS was detected in 10 patients (25%), while T2* value was lower than 20 ms in 10 patients (25%). The mean age of patients with and without fQRS was 26.23 $\pm$ 2.71 and 19.40 $\pm$ 2.61 years, respectively (P = 0.001). The univariate analysis indicated that fQRS had a significant relationship with cardiac iron overload (OR = 5; 95% CI: 1.04 - 23.99; P < 0.044). The multiple logistic regression analysis represented a significant association between iron overload and fQRS (OR = 5.556; 95% CI: 1.027 - 30.049). The sensitivity and specificity of the fQRS against MRI were equal to 50% and 83.3% respectively.
Conclusions: The absence of fQRS on ECGs could be a good predictor of the lack of cardiac iron overload in β-TM patients. The results showed that fQRS might indicate the no need for close monitoring for cardiac overload with cardiac MRI and aggressive chelation therapy.

Keywords: Beta-Thalassemia Major, Electrocardiography, Fragmented QRS, Cardiac MRI, T2* Value

1. Background

Beta-thalassemia major (β-TM) is recognized as a common monogenic disorder, reducing globin synthesis. Frequent blood transfusions are necessary for β-TM patients due to deep anemia associated with unsuccessful erythropoiesis. Cardiac iron overload in these patients is recognized as the most important cause of cardiac arrhythmias (1, 2). To evaluate cardiac iron load, it is suggested to regularly measure cardiac magnetic resonance (MR) and T2* value (3, 4). However, since MRI is a costly and complex method for early detection of cardiac disorders, physicians are seeking more practical approaches.

Cardiac iron overload is related to non-homogeneous myocardial activation in β-TM patients. Fragmented QRS (fQRS) is described as a suitable myocardial scar marker, measured by 12-lead electrocardiograms (ECGs). It is defined as additional spikes within the QRS complex, representing a conduction delay due to inhomogeneous ventricular activation, resulting from a myocardial scar. Evidence suggests that fQRS is related to ventricular tachyarrhythmia (5, 6). This arrhythmic marker is mainly used for ischemic etiologies, although it has been frequently measured in patients with non-ischemic cardiac diseases, especially systemic diseases with cardiac involvement. According to recent research, the presence of fQRS on surface ECGs is indicative of disorders, resulting in non-homogeneous myocardial activation (4).

2. Objectives

The present study aimed at determining the correlation of fQRS in non-homogeneous cardiac activities (e.g., fi-

brosis and scar formation) with cardiac iron overload (cardiac T2* value) in β-TM patients. Moreover, the association of fQRS was examined with the type of iron chelators and cardiac T2* value.

3. Methods

3.1. Study Population

This cross-sectional study included 40 β-TM patients, aged 5 - 40 years, who were admitted to our thalassemia center between September 2017 and April 2018. The sampling method was convenience. This study was approved by Arak University of Medical Sciences (IR.ARAKMU.REC.1395.208). Written informed consents were also obtained from the parents or the patients.

3.2. Eligibility

All the patients regularly received iron chelators and blood transfusions. We divided the patients into four groups: deferiprone, deferasirox, deferoxamine, and deferiprone + deferoxamine. The exclusion criteria were as follows: hypertension; diabetes mellitus; ischemic heart disease; and smoking.

3.3. Electrocardiographic and Cardiac MRI Measurements

The presence of fQRS was examined on 12-lead surface ECGs. The pattern of fQRS was described as the identification of different RSR' patterns in the absence or presence of Q wave in two nearby derivations; additional R wave or notching in the nadir of R or S wave; or the presence of more than one R wave in the absence of typical bundle branch block. Standard 12-lead ECGs were examined without any magnification. If a detectable signal was found in particular lead complexes, fragmentations were identified. Also, fQRS was considered to be present if it was found in two lateral, anterior, or inferior leads. In addition, cardiac iron overload, which was defined as T2* value below 20 ms, was examined using cardiac T2* MRI. The fQRS evaluated by one pediatric cardiology and the cardiac MRI reported by one radiologist who was expert in cardiac MRI. The pediatric cardiologist did not aware about the Cardiac MRI reports.

3.4. Statistical Methods

For data analysis was performed with the IBM SPSS version 23 for Windows (IBM SPSS Inc, Chicago, IL, USA). Frequency and percentage were measured to present the categorical variables. For comparison of categorical variables were used chi-square and Fisher's exact tests, while independent samples *t*-test was applied for continuous variables. In addition, the risk factors were identified based on multiple logistic regression. Also, we have measured confidence intervals (95% CI) as well as the sensitivity and specificity of the fQRS against MRI. The P value less than 0.05 was regarded as statistical significant.

4. Results

A total of 40 β-TM patients were evaluated, including 17 men. The patients' mean age was reported to be 22.45 $\pm$ 6.75 years. Patients with and without cardiac involvement showed no significant difference regarding gender, age, or left ventricular ejection fraction (Table 1).

The association between cardiac T2* value and fQRS on ECGs was confirmed. Based on the findings, fQRS was detected in 10 patients (25%), while T2* value was below 20 ms in 10 patients (25%). The mean age of samples with and without fQRS was 26.80 $\pm$ 6.34 and 21.00 $\pm$ 6.33 years, respectively (P = 0.017). The groups with and without fQRS were not significantly different regarding the left ventricular ejection.

Sensitivity and specificity of the fQRS against MRI was equal to 50% and 83.3% respectively. The association of fQRS with cardiac iron overload was examined using logistic regression analysis. A significant correlation was found between these variables in the univariate analysis (OR: 5; 95% CI: 1.04 - 23.99; P < 0.044). Also, the importance of iron chelators was determined in a univariate analysis. The patients who received deferiprone showed major cardiac involvement in comparison with patients receiving other chelators (Table 2). The univariate analysis indicated that patients with fQRs had major cardiac involvement (Table 3).

According to the multiple logistic regression, fQRS had a significant correlation with cardiac iron overload Therefore, detection of fQRS in β-TM patients can predict cardiac iron overload (Table 4).

5. Discussion

In 12-lead ECGs, a suitable marker of the myocardial scar is fQRS, which is described as an additional spike of QRS complexes without bundle branch block. There are multiple RSR' patterns in the inferior or middle precordial leads. Our findings represented that fQRS on surface ECGs is indicative of increased cardiac iron overload only in half of β-TM patients and the absence of fQRS is an excellent predictor for good situation cardiac. Previous studies show that iron accumulation mainly occurs in the myocardium. Generally, for the measurement of iron overload, it is suggested to determine cardiac MR and T2* value.

Table 1. Demographics of Patients with and without Cardiac Involvement

	Cardiac MR T2* < 20 ms (N = 10)	Cardiac MR T2* > 20 ms (N = 30)	P Value
Age, y	26.40 ± 5.64	21.13 ± 6.65	0.031*
Gender, F/M	6/4	17/13	0.853
Hemoglobin, g/dL	9.07 ± 0.52	9.38 ± 0.79	0.258
White blood cell count, 10^3/mm^3	8.67 ± 4.13	7.12 ± 4.34	0.329
Platelet, 10^3/mm^3	408 ± 10	425 ± 87	0.302
fQRS, No. (%)	5 (50)	5 (16.7)	0.035
T2* value	15.27 ± 4.22	27.53 ± 5.14	0.0001*
Left ventricular end diastolic diameter, mm	48.12 ± 4.67	47.73 ± 3.98	0.798
Left ventricular end systolic diameter, mm	32.11 ± 3.67	31.45 ± 2.57	0.532
Ejection fraction	54.67 ± 10.45	55.34 ± 8.71	0.842

Abbreviations: fQRS, fragmented QRS

Table 2. The Correlation of Iron Chelators and Cardiac Involvement with fQRS

	With fQRS (N = 10)	Without fQRS (N = 30)	P Value
Age	26.80 ± 6.34	21.00 ± 6.33	0.017
Deferiprone	5	1	0.002*
Deferoxamine	2	10	0.693
Deferiprone + deferoxamine	1	8	0.404
Deferasirox	2	11	0.451

Table 3. The Association Between Cardiac Iron Overload and fQRS

	With fQRS (N = 10)	Without fQRS (N = 30)	P Value
T2* < 20 ms	8	0	0.0001*
T2* > 20 ms	2	28	0.0001*

Table 4. Multiple Logistic Regression Analysis of Cardiac T2* MR

	OR	95% CI	P Value
Ferritin	1.001	1.001 - 1.002	0.105
fQRS	5.556	1.027 - 30.049	0.046*
Hemoglobin	0.600	0.203 - 1.777	0.357

Abbreviations: fQRS, fragmented QRS

Cardiac iron overload seems to interrupt or block myocardial electrical conduction and lead to myocardial contraction disorders. Early stages of the disease are associated with bradycardia, changes in the ST-T segment, premature ventricular and atrial systoles, left ventricular hypertrophy, and first-degree atrioventricular blockade. On the other hand, complete or second-degree atrioventricular blockade, premature atrial and ventricular contractions, and supraventricular tachycardia may occur in the late stages. Previous findings suggest that slow conduction in cardiac muscles prolongs QT and PR intervals (7).

The conditions of are associated with non-homogeneous myocardial activation (e.g., fibrosis), can produce fQRS on ECGs. According to previous findings, fQRS represents conduction delays associated with inhomogeneous ventricular activation because of myocardial scar. The evidence suggests that low T2* values represent disorders in the myocardial conduction system. In this regard, a study on 652 β-TM patients showed the risk of arrhythmia in patients with cardiac T2* values below 20 ms. The risk of cardiac insufficiency was also reported in cases with T2* values below 10 ms (8). In the present study, we assessed fQRS and there was only 50% patients at cardiac T2* values below 20 ms. Our finding was varied according to the previous study.in other words, based on our findings; it was found that absence was much more valuable and useful.

The incidence of fQRS increased with age in the present study, which is suggestive of time-dependent fibrosis. In another study, ventricular late potential (VLP) was found to be more common in β-TM patients. Also, in patients with VLP, premature ventricular systoles, as well as transient ventricular tachycardia, were frequent (9). Normally, β-TM patients, receiving inadequate chelation therapy, experience cardiac insufficiency. It is known that excess free iron, which is undeposited in the lysosomes, has toxic effects on the cells. Moreover, it interrupts redox reactions, as well as gene changes, and triggers free radical formation, resulting in the oxidative impairment of membranes. Consequently, cardiac dysfunction occurs due to impaired mitochondrial energy production (10, 11).

In β-TM patients, the most important cause of mortality is cardiac insufficiency; therefore, timely detection

of cardiac problems and treatment modifications are of great significance. In these patients, non-uniformity of the left ventricular wall is an early indicator of cardiac involvement, despite intact global ventricular function. In the present study, we first assessed cardiac function using M-mode echocardiography. No cardiac dysfunction was found on traditional echocardiography. Next, the participants were classified into two groups, and ejection fraction and ventricular diameters were measured. The groups showed no significant difference, except for age, which might indicate a time-dependent process in these patients (Table 1).

Electrical heterogeneity in the ventricular myocardium may account for the inhomogeneous deposition, oxidative mechanisms, and localized fibrous replacement. Nevertheless, the mechanisms of fQRS development remain unclear, although fQRS seems to be associated with non-homogeneous depolarization in disorders, such as fibrosis, myocardial scar, and ischemia (12). Previous research suggests fQRS evaluation as a helpful tool for the assessment of cardiac risk and arrhythmic events. Moreover, in another study on ST-segment elevation myocardial infarction, fQRS on ECGs could help identify high-risk patients (13, 14).

The association of cardiac iron overload with fQRS on surface ECGs predicted based on our findings. On based our study, 50% of patients with T2 less than 20 had abnormal ECG, whereas in T2 more than 20 only 16% had an abnormality in ECG tracing. This finding suggested that effecting predictor fQRS is significant.

It is generally important to evaluate the emergence of fQRS on surface ECGs during follow-ups in order to modify the treatment regimens accordingly. Also, age was found to have a significant association with low T2* and fQRS, suggesting an absence of cardiac iron load with age. In another study, delayed-enhancement cardiac MRI was used to examine myocardial scars in 115 TM patients. Delayed-enhancement regions were detected in 28 patients (24%), 26 of whom showed patchy fibrosis. Scar formation was mostly found in older patients. Also, TM patients showed more frequent myocardial fibrosis and necrosis, compared with the normal population (15).

Regarding the type of iron chelators, fQRS was less commonly detected in patients receiving deferoxamine or deferasirox. In the present study, deferasirox (Exjade) and deferoxamine were more suitable than other chelators, and T2* values were above 20 ms (Table 5). Moreover, a logistic regression analysis indicated a significant association between fQRS and cardiac iron overload. The results showed that cardiac iron overload was five times more common among patients with fQRS.

Nermin Bayar et al found of total of 103 patients (mean age 22.6 $\pm$ 6.6) with diagnosis of beta thalassemia major, 50 patients (48%), fQRS detected, 37 of them (74%), T2* values were found to below. the presence of fQRS, low T2* value to predict the sensitivity of 86.0% and specificity of 78.3%, respectively (16). In our study, presence of fQRS was 50% in T2* value less than 20.

In the present study, fQRS was not observed in 28 patients with T2* values exceeding 20 ms. Univariate analysis was used to determine the association between cardiac involvement and fQRs. Increased iron overload was associated with a high incidence of fQRS. Also, the importance of iron chelators in cardiac involvement was examined based on the univariate analysis. The results revealed the high incidence of cardiac involvement in patients receiving deferiprone, compared with others. Iron deposition was not significantly different between the recipients of different chelators. In our study, it was found that the combination of deferiprone and deferoxamine is more suitable than other chelators and that the presence of fQRS was less common in these patients.

Based on the multiple logistic regression analysis, cardiac iron overload and fQRS were significantly correlated. This finding suggests the high predictive value of fQRS for cardiac iron overload in TM patients; in fact, cardiac iron overload was 5.5 times more common among patients with fQRS. Of course, we cannot express detecting fQRS in ECG tracing is the only relating to iron overload.

However, we recommend performing cardiac imaging based on the proposed protocols, to further studies and long-term follow-up in patients with thalassemia major. Therefore, the fQRS cannot substitute cardiac MRI and T2* should still be done in all patients and fQRS only can be considered if MRI cannot be done in such patients.

Finally, it should be kept in mind that fQRS can also occur for other causes, for example, cardiac ischemia related to myocardial scar/myocardial ischemia or myocardial fibrosis.

The fQRS is to be a good predictor of cardiac events due to CAD and patients with acute MI (17). Also in patients with non-ischemic cardiomyopathy, fQRS is related to a degree of fibrosis and dys-synchrony and influences the response for CRT (1).

At result, we should considers other causes of fQRS changes in patient thalassemia, such as fQRS is a marker of myocardial scar in coronary artery disease (CAD), arrhythmic events in non-ischemic cardiomyopathy, no ischemic cardiomyopathy (NICM), arrhythmogenic right ventricular dysplasia /cardiomyopathy (ARVD/C), Brugada syndrome, acquired long QT syndrome and cardiac sarcoidosis (18).

The fQRS has reported in case of mitral stenosis, decreased mitral valve area and also in patients with mitral

Table 5. Iron Chelators Used for Patients with Cardiac Involvement

	Deferiprone	Deferoxamine	Deferiprone + Deferoxamine	Deferasirox (Exjade)
T2* < 20 ms	3	3	1	3
T2* > 20 ms	1	12	7	10
Presence of fQRS (n = 10)	5	2	1	2
Absence of fQRS (n = 30)	1	10	8	11

Abbreviations: fQRS, fragmented QRS

stenosis caused by rheumatic fever. Other causes of fQRS were hypertrophic cardiomyopathy (HCM), left ventricular non-compaction, heart failure associated with low EF, poor NYHA functional class and increased pulmonary pressure (19).

This finding shows that the presentation of fQRS is a nonspecific finding, and its interpretation should only be performed in the presence of clinical manifestations and type of myocardial involvement.

5.1. Conclusions

The results showed that the absence of fQRS on surface ECGs must be considered in β-TM patients to modify treatments as well as aggressive chelation therapy. The absence of fQRS could majorly predict that the cardiac iron overload did not happen. Therefore, absence of fQRS might indicate the importance of no need for close monitoring with cardiac MRI T2*, and aggressive chelation therapy.

5.2. Limitations

First, we could not evaluate the impact of fQRS on prognosis, as we did not perform any follow-up studies. Second, we could not conduct 24-hour Holter monitoring to determine rhythm disorders. Third, we could not use low-pass filters to decrease the electrical and musculature noise during 12-lead ECG recordings, and we did not examine subclinical cardiac dysfunction, based on systolic and diastolic phases of pulsed-wave Doppler echocardiography. Finally, the cardiologist was not blinded considering the patients' general appearance.

Acknowledgments

The authors would like to thank all hematology centers' staff and thalassemia patients in ARAK for their kind cooperation in this study.

Footnotes

Authors' Contribution: Study concept and design: Yazdan Ghandi; analysis and interpretation of data, statistical analysis: Danial Habibi; critical revision of the manuscript for important intellectual content: Aziz Eghbali

Conflict of Interests: The authors declare no conflict of interests.

Ethical Approval: The study protocol was reviewed and confirmed by the Medical Ethics Committee of ARAK University of Medical Sciences approved the study (IR.ARAKMU.REC.1395.208).

Funding/Support: This study was supported by the Deputy of Research, as part by an MD thesis from the School of Medicine, at Arak University of Medical Sciences.

Informed Consent: Written ethical consent was taken from all participants.

References

1. Basaran Y, Tigen K, Karaahmet T, Isiklar I, Cevik C, Gurel E, et al. Fragmented QRS complexes are associated with cardiac fibrosis and significant intraventricular systolic dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS interval. *Echocardiography*. 2011;**28**(1):62–8. doi: 10.1111/j.1540-8175.2010.01242.x. [PubMed: 20618390].
2. Ghandi Y, Eghbali A, Rafie F. Correlation between mean serum ferritin levels and atrial electrocardiographic markers in beta-thalassemia major. *Iran J Blood Cancer*. 2018;**10**(3):76–81.
3. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation*. 2006;**113**(21):2495–501. doi: 10.1161/CIRCULATIONAHA.105.595892. [PubMed: 16717150].
4. Westwood M, Anderson LJ, Firmin DN, Gatehouse PD, Charrier CC, Wonke B, et al. A single breath-hold multiecho T2* cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload. *J Magn Reson Imaging*. 2003;**18**(1):33–9. doi: 10.1002/jmri.10332. [PubMed: 12815637].
5. Chatterjee S, Changawala N. Fragmented QRS complex: A novel marker of cardiovascular disease. *Clin Cardiol*. 2010;**33**(2):68–71. doi: 10.1002/clc.20709. [PubMed: 20186984]. [PubMed Central: PMC6653133].
6. Buyukkaya E, Karakas MF, Kurt M, Bilen P, Yalcin F, Celik M, et al. The relation of fragmented QRS with tissue Doppler derived parameters in patients with b-thalassaemia major. *Clin Invest Med*. 2012;**35**(5). E334. doi: 10.25011/cim.v35i5.18707. [PubMed: 23043715].

7. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation*. 2009;**120**(20):1961–8. doi: 10.1161/CIRCULATIONAHA.109.874487. [PubMed: 19801505]. [PubMed Central: PMC2784198].
8. Ghandi Y, Sharifi M, Eghbali A, Habibi D. Effect of average annual mean serum ferritin levels on QTc interval and QTc dispersion in beta-thalassemia major. *Int J Pediatr*. 2017;**5**(8):5431–40.
9. Franzoni F, Galetta F, Di Muro C, Buti G, Pentimone F, Santoro G. Heart rate variability and ventricular late potentials in beta-thalassemia major. *Haematologica*. 2004;**89**(2):233–4. [PubMed: 15003899].
10. Wood JC. Cardiac iron across different transfusion-dependent diseases. *Blood Rev*. 2008;**22 Suppl 2**:S14–21. doi: 10.1016/S0268-960X(08)70004-3. [PubMed: 19059052]. [PubMed Central: PMC2896332].
11. Aessopos A, Farmakis D, Andreopoulos A, Tsironi M. Assessment and treatment of cardiac iron overload in thalassemia. *Hemoglobin*. 2009;**33 Suppl 1**:S87–92. doi: 10.3109/03630260903347401. [PubMed: 20001638].
12. Kirk P, Carpenter JP, Tanner MA, Pennell DJ. Low prevalence of fibrosis in thalassemia major assessed by late gadolinium enhancement cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2011;**13**:8. doi: 10.1186/1532-429X-13-8. [PubMed: 21241474]. [PubMed Central: PMC3025880].
13. Stoyanova E, Cloutier G, Felfly H, Lemsaddek W, Ah-Son N, Trudel M. Evidence for a novel mechanism independent of myocardial iron in beta-thalassemia cardiac pathogenesis. *PLoS One*. 2012;**7**(12). e52128. doi: 10.1371/journal.pone.0052128. [PubMed: 23284899]. [PubMed Central: PMC3524169].
14. Kocaman SA, Cetin M, Kiris T, Erdogan T, Canga A, Durakoglugil E, et al. The importance of fragmented QRS complexes in prediction of myocardial infarction and reperfusion parameters in patients undergoing primary percutaneous coronary intervention. *Turk Kardiyol Dern Ars*. 2012;**40**(3):213–22. doi: 10.5543/tkda.2012.36937. [PubMed: 22864316].
15. Pepe A, Positano V, Capra M, Maggio A, Pinto CL, Spasiano A, et al. Myocardial scarring by delayed enhancement cardiovascular magnetic resonance in thalassaemia major. *Heart*. 2009;**95**(20):1688–93. doi: 10.1136/hrt.2008.156497. [PubMed: 19491092].
16. Bayar N, Kurtoğlu E, Arslan Ş, Erkal Z, Deveci B, Yüksel İÖ, et al. The Importance of Fragmented QRS in Evaluation of Cardiac Iron Burden, in Patients with β-Thalassemia Major. *J Am Coll Cardiol*. 2013;**62**(18):C152. doi: 10.1016/j.jacc.2013.08.451.
17. Wang DD, Buerkel DM, Corbett JR, Gurm HS. Fragmented QRS complex has poor sensitivity in detecting myocardial scar. *Ann Noninvasive Electrocardiol*. 2010;**15**(4):308–14. doi: 10.1111/j.1542-474X.2010.00385.x. [PubMed: 20946552]. [PubMed Central: PMC6931930].
18. Das MK, Zipes DP. Fragmented QRS: A predictor of mortality and sudden cardiac death. *Heart Rhythm*. 2009;**6**(3 Suppl):S8–14. doi: 10.1016/j.hrthm.2008.10.019. [PubMed: 19251229].
19. Jain R, Singh R, Yamini S, Das MK. Fragmented ECG as a risk marker in cardiovascular diseases. *Curr Cardiol Rev*. 2014;**10**(3):277–86. doi: 10.2174/1573403x10666140514103451. [PubMed: 24827794]. [PubMed Central: PMC4040879].